REMARKS/ARGUMENTS

Interview Summary by Applicants

Applicants express their appreciation to Examiners Gibbs and Epps-Ford for the courtesy of the telephonic interview conducted on Thursday, June 23, 2005. Prior to this interview, Applicants provided copies of (a) a draft amendment to claim 1 to specify that the oligonucleotide recited therein is non-cleaving; and (b) a draft Rule 132 Declaration executed by a joint inventor discussing the relevance of the McLean document cited by the Examiner in the second 103(a) rejection to the present application.

During the interview, Applicants discussed pending claims 1, 5, 7, 9-13 and 15 and the outstanding 102(b) and 103(a) rejections applied thereto. No decisions were reached regarding the 103(a) rejections. Applicants were advised that the Examiner would not enter these amendments and arguments in an After Final paper, but would consider the same if filed with a Request for Continued Examination.

In this interview, Applicants specifically discussed the following points:

(i) Applicants proposed canceling claim 11 to moot the outstanding 102(b) rejection over Bennett et al. (US Patent No. 6,008,344).

(ii) Applicants proposed to amend claim 1 to require that the oligonucleotide is "non-cleaving" and discussed that this embodiment is inherently and implicitly taught in the specification, as discussed in detail below.

(iii) Applicants proposed that the amendment to claim 1 should overcome the first 103 rejection over McLean

et al. (Nature, 1987 330: 132-137) in view of Morishita et al. (Circulation, 1998 98:1898-1904), Baracchini et al. (US Patent No. 5,801,154), and McKay et al. (US Patent No. 6,258,601) since Morishita only discussed ribozymes that are cleaving.

(iv) Applicants also discussed the second 103(a) rejection over McLean in view of Prosnyak et al., 1994 Genomics, 3:490-494 (Prosnyak) or Deverre et al., 1997 Nucl. Acids Res., 25:3584-3589) and that the 30 nt probe discussed in McLean was not an antisense oligonucleotide. Applicants further discussed the draft Rule 132 Declaration in which one of skill in the art would not have determined that the probe in McLean was antisense. The Maniatis laboratory manual (1989) was discussed in the Rule 132 Declaration as evidence that such probes are typically sense probes.

(v) Finally, Applicants advised the Examiner that US Patent Application No. 10/684,440 was related to the present application and that an Office Action had been issued in that application. Examiner Gibbs asserted that it would not be necessary to provide a copy of the Office Action, but that copies of any new documents cited by the Examiner should be submitted in a Supplemental Information Disclosure Statement (SIDS). Applicants agreed to submit such a SIDS.

Status of Claims

After amendment, claims 1, 5, 7, 9-13 and 15 are pending. Claim 11 is canceled, without prejudice, and Applicants reserve the right to prosecute these claims in a

continuation application filed during the pendency of the present application.

Claim 1 is amended to require that the antisense compounds of the invention are non-cleaving. This non-cleaving embodiment of the invention is inherently supported in the specification and particularly in the description of preferred oligonucleotides at page 8, line 35 through page 9, line 3; page 21, lines 16-24; page 26, lines 4-15; and page 88, Table 1. None of the oligonucleotides which hybridize directly to the target sequence of apolipoprotein(a) SEQ ID NO: 3 have cleaving ability. None of the oligonucleotides exemplified in Table 1 have any catalytic or cleaving regions and thus are examples of non-cleaving oligonucleotides of this invention. Further, it is inconsistent with the function of a primer as suggested on page 26, lines 4-15 for an oligonucleotide to have a cleaving function. Further, the only "cleaving" function ever mentioned in the specification is when the oligonucleotide is a specific type of chimeric compound described on page 21, lines 16-29. By contrast, the other chimeric compounds described at page 21, lines 30-35 and exemplified in the Examples have no cleaving function. Thus, the specification is believed to clearly support the use of the term "non-cleaving".

As the Examiner is aware, MPEP § 2163 provides that there is "...no *in haec verba* requirement..." for newly added claim subject matter and that the same "...must be supported in the specification through express, **implicit**, or **inherent** disclosure" (emphasis added). In view this section and above-noted remarks regarding support in the

specification for "non-cleaving", Applicants assert that identification of the antisense compounds of the invention as "non-cleaving" is well supported by the specification and finds more than adequate written description. While Applicants do not believe that it is necessary to amend the specification to specifically recite that the antisense compounds discussed therein are "non-cleaving" (which is permitted under MPEP § 2163.07(a)), Applicants would be receptive to making such an amendment if so instructed by the Examiner.

35 USC § 102(b) Rejection

Claim 11 is rejected under 35 USC § 102(a) over Bennett et al. (US Patent No. 6,008,344).

The Examiner asserted that the modified antisense oligonucleotide of Bennett is 100% complementary to at least an 8-nucleobase portion of an active site of SEQ ID NO: 3 and noted the 10-nucleobase portion of nucleobases 464-473 of SEQ ID NO: 3.

The cancellation of claim 11 moots the outstanding rejection.

35 USC § 103(a) Rejections

(i) *Claims 1, 5, 7, 9-13, and 15 are rejected under 35 USC § 103(a) over McLean et al. (Nature, 1987 330: 132-137) in view of Morishita et al. (Circulation, 1998 98:1898-1904), Baracchini et al. (US Patent No. 5,801,154), and McKay et al. (US Patent No. 6,258,601).*

The Examiner asserted that while the ribozymes of Morishita do not meet the structural limitation of the claims, they provide the motivation to make antisense oligonucleotide inhibitors to apolipoprotein(a).

The Examiner also asserted that one of skill in the art would have been motivated to make an antisense oligonucleotide targeted to a nucleic acid encoding apolipoprotein(a) using the sequence of McLean and motivation of Morishita with Baracchini, which was cited to provide motivation to make a specific length and modifications of an oligonucleotide and McKay, which was cited to teach antisense include ribozymes as art-recognized functional equivalents.

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason and contend that no combination of the cited art teaches or suggests the present invention.

The combination of McLean and Morishita with Baracchini and McKay[1] does not provide any motivation for one of skill in the art to prepare **non-cleaving** antisense compounds to apolipoprotein(a) as recited in amended claim 1. If one were to combine the apolipoprotein(a) target sequence of McLean with Morishita's ribozyme (i.e., cleaving) oligonucleotides, as suggested by the Examiner, one would effectively provide a composition that cleaves apolipoprotein(a). McKay, Baracchini, and Morishita refer to the existence of non-cleaving oligonucleotides *and* cleaving oligonucleotides (i.e., ribozymes). However, as clearly taught by Morishita (at page 1898, col. 2, last two lines through page 1899, col 1, lines 1-7) and not contradicted by McKay or Baracchini, ribozymes inhibit expression by cleaving the target. Non-cleaving

[1] Applicants note that US Patent No. 6,258,601 is called McKay herein for consistency, but has Monia as its first inventor on the patent coversheet.

oligonucleotides operate by a different mechanism. Thus, adding McKay's or Baracchini's generic teachings that there exist cleaving and non-cleaving oligonucleotides, which may be of a certain length and contain certain modifications and may be directed to other targets, to Morishita's preference for apolipoprotein(a)-directed ribozymes and McLean's apolipoprotein(a) target does not provide the suggestion or motivation for ***non-cleaving*** apolipoprotein(a)-inhibiting oligonucleotides, particularly in the face of Morishita's express teaching away from the non-cleaving oligonucleotides to apolipoprotein(a). See Morishita, page 1899, col. 1, lines 8-14. One of skill in the art would not therefore have been motivated to use the **cleaving** ribozymes of Morishita to prepare **non-cleaving** antisense oligonucletoides to McLean's known sequence of apolipoprotein(a). Specifically, since Morishita teaches ribozymes that one of skill in the art would readily understand are cleavable, one would not be motivated to use to same to make **non-cleaving** antisense oligonucleotide compounds to apolipoprotein(a) by combining the same with McLean. Rather the combination of McLean and Morishita, with Baracchini and McKay teaches the reverse! This combination thereby teaches away from the presently claimed invention.

Reconsideration of this rejection is requested.

(ii) *Claims 1, 5, 9, 11, 12, 13, and 15 are rejected under 35 USC § 103(a) over McLean in view of Prosnyak et al., 1994 Genomics, 3:490-494 (Prosnyak)or Deverre et al., 1997 Nucl. Acids Res., 25:3584-3589).*

> *The Examiner asserted that it would have been obvious to make an oligonucleotide 12-30 nucleobases in length targeted and 100% complementary to a nucleic acid molecule encoding apolipoprotein(a) to use a sequence probe as taught by McLean. One would also have been motivated to modify the probe as taught by Prosnyak and Deverre.*

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reason.

In examining McLean in detail with the assistance of one of the inventors, Applicants wish to clarify and correct a statement made in a prior response and respectfully disagree with the characterization of the synthetic 30-base oligonucletotide probe in McLean that spans the breakpoint of apolipoprotein(a) and plasminogen (Figure 1b at dotted underline) as reverse complementary to nucleobases 80-109 of SEQ ID NO: 3 of Applicants' invention.[2] In fact, nowhere in McLean is it stated that the probe is an antisense sequence. Instead, McLean states that

> "[n]ucleotides 80-109 (.....) ***correspond to*** the synthetic 30 base oligonucleotide used to isolate 5' clones"[3] (emphasis added).

As support, Applicants have provided a Rule 132 executed by Mark J. Graham (hereinafter Mr. Graham), a joint inventor of this application who is skilled in the art of cDNA cloning and probe hybridization. In this Declaration, Mr. Graham has asserted one of skill in the art reading McLean would not necessary conclude that the

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2 Page 8, Paragraph 6 of April 6, 2005 Office Action

3 Page 135, caption for Figure 1, line 18

document teaches or suggests that the 30 nucleobase oligonucleotide probe spanning nucleobases 80-109 is ***reverse complementary*** to the 30 nucleobases target oligonucleotide. Rather the probe referred to by McLean is likely to be identical to the target sequence. See, for the scientific explanation of this argument the attached Declaration.

Therefore, any combination of McLean with Prosnyak and/or Deverre (which refer to generic oligonucleotide modifications useful in a competitive enzyme hybridization assay and modifications for adenine and cytosine residues in DNA fingerprinting assays) would only provide the full-length sequence of apolipoprotein(a) or probes thereof in which the sequence thereof is identical to sequence of a selected portion of apolipoprotein(a).

As such, this combination does not teach or suggest or provide motivation for generating the non-cleaving, apolipoprotein(a) targeting oligonucleotides of the present invention.

Reconsideration of this rejection is requested.

Information Disclosure Statement

Applicants respectfully request that the examiner consider the following documents provided in the attached supplemental IDS:

a. a new document cited by Examiner Bowman in US Patent Application No. 10/684,440's Office Action of January 26, 2005 - Opalinska et al., Nat. Rev., July 2002, 1(7):503-514;

b. a new document cited by Examiner Bowman in US Patent Application No. 10/684,440's Office Action of January 26, 2005 - Green et al., J. Am. Coll. Surg., July 2000, 191(1):93-105;

c. Callow et al., Proc. Natl. Acad. Sci. USA, March 1994, 91:2130-2134;

d. the published PCT application corresponding to the present application (US Patent Application No.09/923,515), namely International Patent Publication No. WO 03/014307; and

e. the published PCT application corresponding to related US Patent Application No. 10/485,113, namely International Patent Publication No. WO 05/000201;

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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